

Hypertrophic Osteoarthropathy in Childhood Malignancy

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Hypertrophic osteoarthropathy (HOA), well known in adults, is rarely encountered in children. The clinical features include clubbing of the fingers and toes, arthritis, and a sometimes painful ossifying periostitis of the tubular bones.

Apart from a hereditary form (primary HOA), most of the cases encountered in children are secondary and associated with conditions such as chronic suppurative lung processes (e.g., cystic fibrosis), congenital heart disease, biliary atresia, and polyposis coli. The association with malignant disorders, which is relatively common in adults, is very rare in children. In 1986 the authors published a case report of a patient with carcinoma of the nasopharynx who developed HOA. Another similar patient has been encountered. In both, the appearance of HOA was associated with a very poor prognosis.

A meticulous research of the literature from 1890 to 1990 revealed only 24 children (19 boys, 5 girls) under the age of 18, with malignancy and associated HOA. Among

them were 10 patients with a carcinoma of the nasopharynx, 8 with osteosarcoma, 3 with Hodgkin's lymphoma, 1 with a periosteal sarcoma, 1 with mesothelioma of the pleura, and 1 with carcinoma of the thymus. In five patients with HOA, there were no abnormalities of the lungs, mediastinum, or pleura, and none developed during the course of the disease.

Many authors mention the predictive value of HOA, especially in association with malignant tumors. In contrast to suppurative processes in the lungs, in those with neoplastic disease involving the chest, HOA may precede pulmonary symptoms by 1-18 months. A striking feature of HOA in these instances is the reversibility of the complaints after successful treatment of the disorder of the chest, both in benign and malignant conditions.

The present case is the second reported by the authors and the first description of a girl with carcinoma of the nasopharynx developing HOA. © 1993 Wiley-Liss, Inc.

Key words: nasopharynx carcinoma, periosteal bone formation, sex preponderance, reversibility of complaints

INTRODUCTION

Hypertrophic osteoarthropathy (HOA) is characterized by clubbing of the fingers and toes, painful swelling of the limbs, periosteal new bone formation along the shafts of the tubular bones of the extremities, arthralgia, and signs of autonomic disorders such as sweating, flushing, and blanching of the skin [1,2]. The underlying causes are manifold, yet the primary precipitating causative agent of this condition is still unknown. HOA was first described by Bamberger in 1889 [3] and Marie in 1890 [4] in association with intrathoracic inflammatory lesions. It can be divided into two forms: 1) primary familial HOA (pachydermoperiostosis), which is transmitted as an autosomal dominant trait, is not associated with pathologic extraskeletal findings, and has distinct radiologic alterations; and 2) secondary HOA, which can be divided into pulmonary and non-pulmonary causes [5]. The more common pulmonary causes include primary lung carcinoma, mesothelioma, and cystic fibrosis. The most frequently associated non-pulmonary causes include congenital heart disease, liver disease, biliary

atresia, venous stasis, inflammatory bowel disease, and polyposis coli [6]. While neoplastic disorders account for 92% of the cases in adults, they have been associated with only 12% of HOA in childhood [7]. After having published a case in 1986 [8], we encountered another child with carcinoma of the nasopharynx developing HOA. We present this new case and compare our findings with those encountered in a comprehensive literature review.

MATERIALS AND METHODS

Case Report

H.B., an 11-year-old girl, was admitted with a swelling at the right side of the neck. A puncture revealed only

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Fig. 1. Radiograph of the right wrist. Distinct periosteal reactions are seen along the shaft of the ulna and the first metacarpal in particular. No signs of bone destruction are discernible.

granulomatous tissue. Five months later a carcinoma of the nasopharynx with lymph node metastasis at the right side of the neck was found. Treatment consisted of 12 weeks of chemotherapy (high doses of methotrexate and cyclophosphamide). No regression occurred. After radiotherapy (7 weeks, 30 Gy) a remission was obtained, lasting for 1.5 years. Then she developed a very painful ossifying periostitis (Fig. 1), leading to the discovery of a recurrence of the nasopharynx carcinoma. A chest X-ray revealed mediastinal lymph node enlargement. The child died 2 months later.

Literature Research

With the help of the CD-ROM computer and working our way through numerous references we retrieved 24 cases which met the following criteria. The children were not older than 17 years, had a proven malignancy, and fitted in with the criteria for HOA mentioned before. Including the present case we reviewed the data of 25 patients. Among them were 11 patients with a carcinoma of the nasopharynx, 8 with an osteosarcoma, 3 with Hodgkin's disease, 1 with a periosteal sarcoma, 1 with mesothelioma of the pleura, and 1 with a carcinoma of the thymus.

RESULTS

The relevant data encountered in the literature were drawn up in Table I, together with the data of the present case.

DISCUSSION

In 1976, Petty et al. [25] reviewed the reported cases of HOA secondary to tumors in childhood. Of the 11 cases he found all were over 11 years of age and 9 were male. Of our 25 cases only 2 were under the age of 10 and 20 were male. So HOA in the first decade is extremely rare and there is a strong sex preponderance. Almost half of the patients had a carcinoma of the nasopharynx as the underlying malignancy. This is very striking because tumors arising in this region account for approximately 1% of all childhood malignancies [31]. Until now all published cases of HOA in children in association with carcinoma of the nasopharynx were male. The present case is the first description of a girl with a carcinoma of the nasopharynx which developed HOA.

In the vast majority of cases the primary malignancy was already known by the time HOA complaints started (see Table I, column a), but the appearance of HOA also led very often to the discovery of manifestations of recurrence or metastasis. This was the case in 15 of 25 patients. In 20 of 25 cases pathologic changes were present on the chest X-ray at the onset of HOA or later. Of these 20 children only 2 had a known survival of more than 18 months after onset of HOA. The other five children, all with a known carcinoma of the nasopharynx, did not show any abnormality on the chest X-ray before or after the onset of HOA. However, no other causes for the development of HOA could be detected. The maximum survival here was 14 months.

Many authors mention the predictive value of HOA, especially in association with malignant tumors, in concordance with our own experience. In contrast to suppurative lung processes, in cases of neoplastic disease of the chest HOA may precede pulmonary symptoms by 1–18 months [32]. Another striking feature of HOA is the reversibility of the complaints after successful treatment of the chest abnormality, both in benign and malignant conditions. This was mentioned in 6 of our 25 cases. In 2 of them the duration of the remission was more than 18 months. As is clear from Table I, columns f and h, the onset of HOA is a bad prognostic sign: 19 patients died, or showed extensive metastases at the end of the follow-up. The mean life span of these patients after HOA was discovered was about 9 months; only 1 lived more than 2 years.

The pathogenesis of HOA, 100 years after its first description, is still unknown. Marie [4] suggested that some tumors produce a hormone-like substance capable of stimulating periosteal growth. A second theory of

TABLE I. Collected Data

Author	Age (years)	Sex	Malignancy	a	b	c	d	e	f	g	h
Adler and Sharma [9]	12	M	Hodgkin's	10	+	+	-	-	+	-	14
Alexander and Johnson [10]	15	F	Osteosarcoma	28	-	+	-	+	+	-	12
Ameri et al. [11]	11	M	CN ⁱ	0	+	+	-	-	-	+	?
Barta [12]	13	M	PS ^j	6	-	+	-	-	+	-	?
Diner [13]	17	M	CN	6	+	+	-	+	+	-	19
Djian et al. [14]	17	M	CN	26	-	-	+	-	-	+	9
Firooznia et al. [15]	14	F	Osteosarcoma	4	+	+	-	-	+	-	8
Flueckiger et al. [16]	14	M	Osteosarcoma	36	+	+	-	+	-	+	2
Hall [17]	13	M	Osteosarcoma	23	+	+	-	-	+	-	13
Hamza et al. [18]	13	M	CN	5	+	-	+	-	-	+	?
Howard et al. [19]	9	M	Osteosarcoma	17	+	+	-	-	+	-	5
Kay et al. [20]	11	M	Hodgkin's	0	+	+	-	-	-	+	?
Ladeb et al. [21]	11	M	CN	4	-	-	+	-	+	-	14
Martin [22]	15	M	CN	6	-	-	+	-	+	-	6
Miller [23]	14	M	CT ^k	0	+	+	-	-	+	-	6
Palugay [24]	13	M	Osteosarcoma	23	-	+	-	-	+	-	5
Petty et al.-1 [25]	11	M	Osteosarcoma	18	+	+	-	+	+	-	3
Petty et al.-2 [25]	13	F	Osteosarcoma	3	+	+	-	-	+	-	3
Pichler et al. [26]	13	M	CN	12	-	+	-	-	+	-	6
Razon-Veronesi and Mazzola [27]	4	M	MP ^l	0	+	+	-	+	-	+	?
Shapiro and Zvaifler [28]	16	F	Hodgkin's	1	-	+	-	-	+	-	1
Staalman [8]	13	M	CN	6	+	+	-	-	+	-	3
Zornoza et al.-1 [29]	14	M	CN	3	-	-	+	-	+	-	12
Zornoza et al.-2 [29]	11	M	CN	9	-	+	-	+	+	-	31
Present case	11	F	CN	18	+	+	-	-	+	-	2

^aFollow-up after initial diagnosis until onset of HOA in months.

^bHOA complaints leading to discovery of recurrence or metastasis.

^cAbnormalities on chest X-ray at onset of HOA, or later.

^dNo abnormalities on chest X-ray at all.

^eReversal of HOA complaints after treatment.

^fPatient died, or showed extensive metastases.

^gFinal outcome unknown.

^hFollow-up after onset of HOA in months.

ⁱCN = carcinoma of the nasopharynx.

^jPS = periosteal sarcoma.

^kCT = carcinoma of the thymus.

^lMP = mesothelioma of the pleura.

Unfortunately we were not able to translate the article of Stol'tser [30] of a child with a schwannoma of the lung which developed HOA.

pathogenesis suggests that arteriovenous shunts allow the escape of an unknown hormone or toxin into the systemic circulation of patients with primary pulmonary disease, pulmonary tumors, and metastatic lesions thus resulting in HOA. A third theory of pathogenesis suggests a neuronal mechanism.

Afferent impulses traveling through the vagal or intercostal nerves from the pulmonary lesion to the central nervous system may be responsible for the symptoms of HOA. This theory is clinically supported by the relief of symptoms after vagotomy and after transection of the intercostal nerves [13,19].

CONCLUSIONS

1. HOA is relatively rare in children. HOA in children with a malignant tumor is very rare: 24 published cases in 100 years.

2. In pediatric oncology carcinoma of the nasopharynx is very rare. In 11 of 25 HOA cases, however, the tumor was a carcinoma of the nasopharynx.
3. The appearance of HOA in a child with a tumor always has a very serious meaning: 20 of 25 patients had pulmonary disease at onset of HOA, or later; and 4 of 5 patients without pulmonary disease died within 14 months after onset of HOA.
4. The appearance of HOA is a bad prognostic sign: only 1 2-year survival out of 20 patients.
5. The exact etiology of HOA is still unknown.

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